Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (**Currently Amended**) A recombinant transgenic mouse, wherein targeted cells ~~at least one cell~~ of said mouse initially comprise ~~comprises~~ at least:

(i) **a transgene expressing** one Cre fusion protein comprising sequentially:

- a Cre recombinase protein;
- a hinge region of at least 15 amino acids;
- a polypeptide comprising the ligand-binding domain of the human nuclear estrogen receptor, or of a vertebrate nuclear estrogen receptor, said polypeptide exhibiting at least one mutation relative to the wild-type form of said ligand-binding domains,

said Cre fusion protein having a negligible, or even zero, recombinase activity in ~~the presence of a natural ligand~~ **the absence of a synthetic ligand endowed with antiestrogenic activity,** and ~~a recombinase activity~~ **the recombinase activity being** induced by ~~small quantities~~ **low dose** of **the** synthetic ligand ~~endowed with antiestrogenic activity~~;

(ii) one or more gene or intergenic DNA sequences of interest naturally belonging to said genome of said mouse, said DNA sequence(s) of interest being flanked by one or more recognition sites ~~[[of]]~~ **for** said Cre recombinase protein, and being located in one or more of the chromosomes of the genome of said cell;

and wherein said mouse has undergone a site-specific somatic recombination of said DNA sequences after administration of a low dose of said synthetic ligand, said synthetic ligand having induced specific recombination of said DNA sequences by said Cre fusion protein in at least 90% of the targeted cells of said mouse, whereas less than 5% of the targeted cells underwent recombination of said DNA sequences in the absence of said synthetic ligand

~~wherein the recombinase targets and specifically inactivates said DNA sequences of interest in the presence of synthetic ligand~~.

2. (Canceled)

3. (Canceled)

4. (Previously Presented) Transgenic mouse according to Claim 1, wherein said sites of recognition specific for said Cre recombinase protein comprise the sequences Lox P.

5. (Previously Presented) Transgenic mouse according to Claim 1, wherein said hinge region comprises all or part of the D hinge region of a nuclear estrogen receptor.

6. (Previously Presented) Transgenic mouse according to Claim 5, wherein said hinge region comprises amino acids 282 to 301 of the sequence SEQ ID No. 2.

7. (Previously Presented) Transgenic mouse according to Claim 1, wherein said polypeptide chosen from the ligand-binding domain of the nuclear human estrogen receptors is the ligand-binding domain of the human nuclear estrogen receptor α and in that said ligand-binding domain exhibits at least the following mutations:

- mutation (G400V) glycine to valine at position 400 of the sequence SEQ ID No. 2;
- mutation (methionine-leucine) to (alanine-alanine) situated at position 543-544 (M543A/L544A mutation) of the sequence SEQ ID No. 2.

8. (Currently Amended) Transgenic mouse according to ~~any~~ Claim 1, wherein said fusion protein is encoded by a fusion gene integrated into one or more of the chromosomes of said cell of said mouse, said fusion gene being under the control of expression elements ensuring its expression in ~~at least one~~ the targeted cells of said mouse.

9. (Withdrawn) Organism according to Claim 1, characterized in that said fusion protein is encoded by a fusion gene integrated into an extrachromosomal expression vector, said fusion gene being under the control of expression elements ensuring its expression in at least one cell of said organism.

10. (Previously Presented) Transgenic mouse according to Claim 8, wherein said expression elements are chosen from elements controlling tissue-specific and cell-specific expression or ubiquitous expression.

11. (Previously Presented) Transgenic mouse according to Claim 8, wherein said elements controlling expression are chosen from elements controlling expression ensuring constitutive expression or elements controlling expression ensuring inducible expression.

12. (Previously Presented) Transgenic mouse according to Claim 8, wherein said expression element is chosen from the group composed of the promoter regions of cytokeratin 14 (K 14), of cytokeratin 5 (K 5), and of the adipocyte fatty acid binding protein 2 (aP2).

13. (Withdrawn) Organism according to Claim 8, characterized in that said fusion gene having the sequence SEQ ID No. 3 encodes the fusion protein Cre-ER^T having the sequence SEQ ID No. 4.

14. (Previously Presented) Transgenic mouse according to Claim 8, wherein said fusion gene having the sequence SEQ ID No. 5 encodes the fusion protein Cre-ER^{T2} having the sequence SEQ ID No. 6.

15. (Withdrawn) Organism according to Claim 8, characterized in that said fusion gene having the sequence SEQ ID No. 7 encodes the fusion protein Cre-ER^{T3} having the sequence SEQ ID No. 8.

16. (Withdrawn) Organism according to Claim 9, characterized in that said fusion gene preferably comprises in the 5' → 3' direction:

- a DNA fragment encoding the Cre recombinase of bacteriophage P1 or one of its variants;
- a DNA fragment of at least 45 nucleotides encoding at least either all or part of the D hinge region of a nuclear estrogen receptor, or a peptide which is functionally equivalent to said D hinge region; and
- a DNA fragment encoding the ligand-binding domain (LBD) of a nuclear estrogen receptor or variants thereof, said DNA fragment having at least one mutation conferring on LBD the capacity to respond to synthetic antiestrogens, but not to natural estrogenic agonists.

17. (Withdrawn) Organism according to Claim 1, characterized in that said fusion protein is introduced into at least one cell of said organism.

18. (Withdrawn) Organism according to Claim 1, characterized in that said synthetic ligand endowed with antiestrogenic activity inducing the activity of the recombinase is chosen from the group composed of Tamoxifen, 4-hydroxyTamoxifen, ICI 164 384 and ICI 182 780.

19. (Previously Presented) Transgenic mouse according to Claim 1, wherein said DNA sequence of interest is a gene comprising RXRα.

20. (Canceled)

21. (Withdrawn) Organism according to Claim 20, characterized in that at least one of the cells of said mouse comprises:

- a fusion gene encoding the fusion protein Cre-ER^T having the sequence SEQ ID No. 4, or Cre-ER^{T2} having the sequence ID No. 6, or Cre-ER^{T3} having the sequence ID No. 8, said fusion gene being under the control of the cytokeratin K5 promoter region;
- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked ("floxed") by a lox site.

22. (Withdrawn) Organism according to Claim 20, characterized in that at least one of the cells of said mouse comprises:

- a fusion gene encoding the fusion protein Cre-ER^T having the sequence SEQ ID No. 4, or Cre-ER^{T2} having the sequence ID No. 6, or Cre-ER^{T3} having the sequence ID No. 8, said fusion gene being under the control of the cytokeratin K14 promoter region;
- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked ("floxed") by a lox site.

23. (Currently Amended) Transgenic mouse according to Claim 1, wherein at least one of the targeted cells of said mouse comprise: ~~comprises:~~

- a fusion gene encoding the fusion protein Cre-ER^{T2} having the sequence ID No. 6, said fusion gene being under the control of the adipocyte fatty acid binding protein 2 (aP2) promoter region;

- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked ("floxed") on each side by one lox site, the two lox sites being oriented as a direct repeat.

24. (Withdrawn) Organism according to Claim 20, characterized in that at least one of the cells of said mouse comprises:

- a fusion gene encoding the fusion protein Cre-ER^{T} having the sequence SEQ ID No. 4, or Cre-ER^{T2} having the sequence ID No. 6, or Cre-ER^{T3} having the sequence ID No. 8, said fusion gene being under the control of the α-1-antitrypsin promoter region;
- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked ("floxed") by a lox site.

25. (Withdrawn) Method of preparing a metazoan organism according to Claim 1, characterized in that it comprises the following steps:

a) obtaining an embyronic stem (ES) cell modified by insertion of site(s) of recognition for said recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) introducing said modified embryonic stem cell into an embryo of said organism;

c) developing said embryo up to the stage of a fertile adult organism;

d) crossing said fertile adult organism with a transgenic organism in which at least one of the cells expresses said fusion protein and obtaining the progeny derived from said crossing; and

e) optionally, selecting, among said progeny, said metazoan organism.

26. (Withdrawn) Method of preparing a metazoan organism according to Claim 1, characterized in that it comprises the following steps:

a) obtaining a somatic cell modified by insertion of site(s) of recognition for said recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) transferring the nucleus of said modified somatic cell into the cytoplasm of an enucleated recipient oocyte;

c) developing the embryo obtained in step b) up to the stage of a fertile adult organism;

d) crossing said fertile adult organism with a transgenic organism in which at least one of the cells expresses said fusion protein and obtaining the progeny derived from said crossing; and

e) optionally, selecting, among the progeny, said metazoan organism.

27. (Withdrawn) Method of preparing a metazoan organism according to Claim 1, characterized in that it comprises the following steps:

a) obtaining an embyronic stem (ES) cell modified by insertion of site(s) of recognition for said recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) introducing said modified embryonic stem cell into an embryo of said organism;

c) developing said embryo; and

d) introducing said fusion protein into at least one cell of said embryo or of the organism obtained from the development of said embryo.

28. (Withdrawn) Method of preparing a metazoan organism according to Claim 1, characterized in that it comprises the following steps:

a) obtaining a somatic cell modified by insertion of site(s) of recognition for said recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) transferring the nucleus of said modified somatic cell into the cytoplasm of an enucleated recipient oocyte;

c) developing said embryo; and

d) introducing said fusion protein into at least one cell of said embryo or of said organism obtained from the development of said embryo.

29. (Withdrawn) Method of conditional recombination, in particular excision, insertion, inversion, translocation, at the level of the DNA sequence of interest into which there is (are) inserted one or more sites of recognition for said recombinase protein, said DNA sequence of interest being located in one or more of the chromosomes of said genome of said cell of said organism according to Claim 1, characterized in that it comprises the steps of:

(i) bringing at least one cell of said organism into contact with a synthetic ligand endowed with antiestrogenic activity;

(ii) inducing the activity of the recombinase of said fusion protein by said synthetic ligand.

30. (Withdrawn) Method of conditional deletion of a DNA fragment in which a method of excision according to Claim 29 is used and in which said DNA fragment(s) to be excised is (are) flanked by two recombinase protein recognition sites oriented as a direct repeat.

31. (Withdrawn) Method of obtaining a metazoan organism, with the exception of humans, in which at least one cell possesses an allele of a gene of interest inactivated by a method of conditional deletion and in which the other allele of said gene of interest possesses a mutation, preferably limited, in exon and/or regulatory sequences, said method being characterized in that it makes it possible to obtain, in a metazoan organism, somatic mutations controlled in space and time, and which are limited (point mutations, small deletions or insertion) in exon and/or regulatory sequences, and in that it comprises the steps of:

a) obtaining a metazoan organism in which at least one cell of the germ line comprises said mutation in one of the alleles of said gene of interest;

b) crossing said organism obtained in step a) with an organism according to Claim 1;

c) selecting a progeny whose genome comprises a gene of interest in which one of the alleles possesses a mutation and the other allele

possesses at least two recombinase protein recognition sites oriented as a direct repeat;

d) using the method according to Claim 30 of conditional deletion, of the DNA fragment of said allele of said gene of interest which is flanked by at least two recombinase protein recognition sites oriented as a direct repeat; and

e) obtaining said metazoan organism in which the genome of at least one cell comprises said gene of interest in which one allele is inactivated, while the other allele possesses a somatic, preferably limited, mutation and preferably in exon and/or regulatory sequences.

32. (Withdrawn) Method according to Claim 29, characterized in that said sites of recognition specific for the recombinase protein are Lox P sites and said recombinase protein is the Cre protein of bacteriophage P1, or one of its variants.

33. **(Currently Amended)** The recombinant ~~Transgenic~~ mouse of Claim 1 capable of being obtained using a method that comprises:

a) obtaining a mouse embryonic stem (ES) cell modified by flanking said DNA sequence(s) of interest, located in one or more chromosomes, with site(s) of recognition for said Cre recombinase protein, by homologous recombination;

b) introducing said modified embryonic stem cell into a mouse embryo;

c) developing said embryo up to the stage of a fertile adult mouse, comprising (i) implanting said embryo into the oviduct of a foster mother mouse to produce a chimeric mouse; and (ii) breeding of said chimeric mouse with a wild-type mouse to produce a mouse which has, in all cells, sites of recognition for said Cre recombinase protein flanking said DNA sequence(s) of interest;

d) crossing said fertile adult mouse with a mouse in which ~~at least one of the~~ targeted cells expresses said Cre fusion protein and obtaining the progeny from said crossing; and

e) ~~optionally,~~ selecting, among said progeny, ~~said transgenic mouse~~ a transgenic mouse comprising both the Cre fusion protein and the one or more gene or intergenic DNA sequences

f) administering to the transgenic mouse obtained in step e) a low dose of a synthetic ligand endowed with antiestrogenic activity in order to induce Cre-mediated recombination.

g) obtaining said recombined transgenic mouse.

34. (Canceled)

35. (Withdrawn) Method of analyzing or studying the biological function of a DNA sequence of interest, in particular of a gene, characterized in that it comprises the steps of:

(i) bringing an organism according to Claim 1 or cells isolated from said organism into contact with a synthetic ligand endowed with antiestrogenic activity;

(ii) optionally inducing the expression of said fusion protein;

(iii) revealing the recombination event catalyzed by the recombinase activity of said fusion protein;

(iv) biochemical and/or physiological and/or phenotypic and/or behavioral study or analysis of said cell or of said organism.

36. (Withdrawn) Method according to Claim 29, characterized in that the bringing of said cells of said organism into contact with said synthetic ligand is carried out according to a route of administration chosen from the oral route, the topical route, injection, in particular intramuscular, intravenous, intracerebral, intraspinal and intraperitoneal injection, or in the case of embryos, fetuses and neonates before weaning by administering said synthetic ligand to the mother.

37. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventive and/or curative treatment of pathological conditions associated with alteration of the expression and/or of the function of said DNA sequence of interest,

characterized in that it comprises the step of administering said compound to an organism according to Claim 1.

38. (Withdrawn) Use of an organism according to Claim 1 or of cells derived from said organism for carrying out a spatiotemporally controlled site-specific recombination of said DNA sequence of interest in its natural chromatin environment, with an efficiency of at least 85%, in the presence of synthetic ligand endowed with antiestrogenic activity in the cells of said organism expressing said fusion protein, and with an efficiency at least lower than 5%, in the absence of synthetic ligand or in the presence of a natural estrogen in the cells of said organism expressing said fusion protein.

39. (Withdrawn) Use according to Claim 38, characterized in that said cells of said organism are chosen from the cells of the epidermis, the hepatocytes and the adipocytes.

40. (Withdrawn) Transgenic mouse K5-Cre-ER^{T}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

41. (Withdrawn) Transgenic mouse K5-Cre-ER^{T2}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

42. (Withdrawn) Transgenic mouse K5-Cre-ER^{T3}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

43. (Withdrawn) Transgenic mouse K14-Cre-ER^{T}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic

activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

44. (Withdrawn) Transgenic mouse K14-Cre-ER^{T2}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

45. (Withdrawn) Transgenic mouse K14-Cre-ER^{T3}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the basal keratinocytes of the epidermis using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alopecia and/or hyperproliferation of the basal keratinocytes and/or an inflammatory reaction of the skin.

46. (Withdrawn) Transgenic mouse αAT-Cre-ER^{T}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the hepatocytes using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse in particular alteration of the proliferation of the hepatocytes.

47. (Withdrawn) Transgenic mouse αAT-Cre-ER^{T2}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the hepatocytes using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse in particular alteration of the proliferation of the hepatocytes.

48. (Withdrawn) Transgenic mouse αAT-Cre-ER^{T3}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the hepatocytes using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse in particular alteration of the proliferation of the hepatocytes.

49. (Withdrawn) Transgenic mouse aP2-Cre-ER^{T}/$RXR_{\alpha}^{L2/L2}$ whose RXR_{α} gene may be selectively inactivated in the adipocytes using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alteration of the metabolism of the lipids in the adipocytes and/or diabetes.

50. **(Canceled)**

51. (Withdrawn) Transgenic mouse aP2-Cre-ER^{T3}/RXR$_\alpha$$^{L2/L2}$ whose RXR$_\alpha$ gene may be selectively inactivated in the adipocytes using a conditional deletion method following treatment with a synthetic ligand endowed with antiestrogenic activity, causing in said mouse alteration of the metabolism of the lipids in the adipocytes and/or diabetes.

52. (Currently amended) Transgenic mouse according to Claim 1, wherein said transgenic mouse is a transgenic mouse aP2-Cre-ER^{T2}/RXR$_\alpha$$^{L2/L2}$, wherein the two floxed alleles of the endogenous RXR$_\alpha$ gene are inactivated by \ conditional excision of a DNA fragment of said RXRα gene, wherein said DNA fragment to be excised is (1) located in two chromosomes of the genome of said cell of said transgenic mouse, and (2) flanked on each side by one recombinase protein recognition site for a Cre recombinase protein, the two recombinase protein recognition sites being oriented as a direct repeat-comprising:

(i) bringing ~~at least one~~ the targeted cells ~~cell~~ of said transgenic mouse into contact with a synthetic ligand endowed with antiestrogenic activity;

(ii) inducing the activity of the recombinase of said fusion protein by said synthetic ligand.

53. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventive and/or curative treatment of alopecia and/or of hyperproliferation of the keratinocytes and/or of inflammatory reactions of the skin, characterized in that it comprises the step of administering said compound to a mouse selected from the group consisting of transgenic mouse K5-Cre-ER^{T}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse K5-Cre-ER^{T2}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse K5-Cre-ER^{T3}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse K14-Cre-ER^{T}/RXR$_\alpha$$^{L2/L2}$, and transgenic mouse K14-Cre-ER^{T2}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse K14-Cre-ER^{T3}/RXR$_\alpha$$^{L2/L2}$.

54. (Withdrawn) Method of screening compounds capable of being used as a medicament for promoting in particular hepatic regeneration, characterized in that it comprises the step of administering said compound to a mouse selected from the group consisting of transgenic mouse αAT-Cre-ER^{T}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse αAT -Cre-ER^{T2}/RXR$_\alpha$$^{L2/L2}$, transgenic mouse αAT -Cre-ER^{T3}/RXR$_\alpha$$^{L2/L2}$.

55. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventive and/or curative treatment of diabetes and/or for the treatment of obesity, characterized in that it comprises the step of administering said compound to a mouse selected from the group consisting of transgenic mouse aP2-Cre-$ER^{T}/RXR_{\alpha}^{L2/L2}$, transgenic mouse aP2-Cre-$ER^{T2}/RXR_{\alpha}^{L2/L2}$, and transgenic mouse aP2-Cre-$ER^{T3}/RXR_{\alpha}^{L2/L2}$.

56. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventive and/or curative treatment of skin cancers, characterized in that it comprises the step of administering said compound to a mouse selected from the group consisting of K5-Cre-$ER^{T}/RXR_{\alpha}^{L2/L2}$, transgenic mouse K5-Cre-$ER^{T2}/RXR_{\alpha}^{L2/L2}$, transgenic mouse K5-Cre-$ER^{T3}/RXR_{\alpha}^{L2/L2}$, transgenic mouse K14-Cre-$ER^{T}/RXR_{\alpha}^{L2/L2}$, and transgenic mouse K14-Cre-$ER^{T2}/RXR_{\alpha}^{L2/L2}$, transgenic mouse K14-Cre-$ER^{T3}/RXR_{\alpha}^{L2/L2}$.

57. (Withdrawn) Method according to Claim 35, characterized in that the bringing of said cells of said organism into contact with said synthetic ligand is carried out according to a route of administration chosen from the oral route, the topical route, injection, in particular intramuscular, intravenous, intracerebral, intraspinal and intraperitoneal injection, or in the case of embryos, fetuses and neonates before weaning by administering said synthetic ligand to the mother.

58. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventative and/or curative treatment of alopecia and/or of hyperproliferation of the keratinocytes and/or inflammatory reactions of the skin, characterized in that it comprises the step of administering said compound to a mouse according to Claim 52.

59. (Withdrawn) Method of screening compounds capable of being used as a medicament for promoting in particular hepatic regeneration, characterized in that it comprises the step of administering said compound to a mouse according to Claim 52.

60. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventative and/or curative treatment of diabetes and/or for the treatment of obesity, characterized in that it comprises the step of administering said compound to a mouse according to Claim 52.

61. (Withdrawn) Method of screening compounds capable of being used as a medicament for the preventative and/or curative treatment of skin cancers, characterized in that it comprises the step of administering said compound to a mouse according to Claim 52.

62. (Canceled)

63. (Canceled)

64. (Canceled)

65. (Canceled)

66. (Currently Amended) Transgenic mouse according to Claim 1, wherein said transgenic mouse is a transgenic mouse aP2-Cre-ER^{T2}/$RXR_{\alpha}^{L2/-}$, wherein the floxed allele of the endogenous RXR_{α} gene is selectively inactivated in adipocytes by conditional excision of a DNA fragment of said RXRα gene, wherein said DNA fragment to be excised is (1) located in one chromosome of the genome of said cell of said transgenic mouse, and (2) flanked on each side by one recombinase protein recognition site for a Cre recombinase protein, the two recombinase protein recognition sites being oriented as a direct repeat, comprising:

(i) bringing targeted cells ~~at least one cell~~ of said transgenic mouse into contact with a synthetic ligand endowed with antiestrogenic activity;

(ii) inducing the activity of the recombinase of said fusion protein by said synthetic ligand.

67. (New) The transgenic mouse of Claim 1, wherein the synthetic ligand endowed with antiestrogenic activity is selected from the group consisting of Tamoxifen, 4-hydroxyTamoxifen, ICI 164 384 and ICI 182 780.

68. (New) The transgenic mouse of Claim 67, wherein the synthetic ligand endowed with antiestrogenic activity is Tamoxifen or 4-hydroxyTamoxifen.

69. (New) A method for producing a spatio-temporally-controlled site-specific somatic recombination in a mouse, wherein one or more gene or intergenic DNA sequences of interest naturally belonging to the genome of said mouse have been recombined, comprising:

a) obtaining a transgenic mouse, wherein targeted cells of said transgenic mouse comprises at least:

(i) a Cre fusion protein comprising sequentially:

- a Cre recombinase protein;
- a hinge region of at least 15 amino acids;
- a polypeptide comprising the ligand-binding domain of the human nuclear estrogen receptor, or of a vertebrate nuclear estrogen receptor, said polypeptide exhibiting at least one mutation relative to the wild-type form of said ligand-binding domains,

said Cre fusion protein having a negligible, or even zero recombinase activity in the absence of a synthetic ligand endowed with antiestrogenic activity, and the recombinase activity being induced by low dose of the synthetic ligand;

(ii) said one or more gene or intergenic DNA sequences of interest, naturally belonging to the cell genome, which are flanked by one or more recognition sites for said Cre recombinase protein, and which are located in one or more of the chromosomes of the genome of said cell;

b) administering to said transgenic mouse a low dose of said synthetic ligand in order to induce Cre-mediated recombination; and

c) obtaining a recombined mouse, wherein said mouse has undergone a site-specific somatic recombination of said DNA sequences after induction, by said synthetic ligand, of specific recombination of said DNA sequences by said Cre fusion protein in at least 90% of the targeted cells of said mouse, whereas less than 5% of the targeted cells underwent recombination of said DNA sequences before step b).

70. (New) A method of making a transgenic mouse according to step a) of Claim 69, said method comprising

(i) obtaining a mouse embryonic stem (ES) cell modified by flanking said DNA sequence(s) of interest, located in one or more chromosomes,

with site(s) of recognition for said Cre recombinase protein, by homologous recombination;

(ii) introducing said modified embryonic stem cell into a mouse embryo;

(iii) developing said embryo up to the stage of a fertile adult mouse, comprising (x) implanting said embryo into the oviduct of a foster mother mouse to produce a chimeric mouse; and (xx) breeding of said chimeric mouse with a wild-type mouse to produce a mouse which has, in all cells, sites of recognition for said Cre recombinase protein flanking said DNA sequence(s) of interest;

(iv) crossing said fertile adult mouse with a transgenic mouse in which targeted cells expresses said Cre fusion protein and obtaining the progeny from said crossing; and

(v) selecting, among said progeny, a transgenic mouse comprising both the fusion protein and the one or more gene or intergenic DNA sequences.

71. (New) A method of producing a transgenic mouse according to step a) of Claim 69, comprising the following steps:

a) obtaining a somatic cell modified by insertion of site(s) of recognition for said Cre recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) transferring the nucleus of said modified somatic cell into the cytoplasm of an enucleated recipient oocyte;

c) developing the embryo obtained in step b) up to the stage of a fertile adult mouse, comprising (i) implanting said embryo into the oviduct of a foster mother mouse to produce a chimeric mouse; and (ii) breeding of said chimeric mouse with a wild-type mouse to produce a mouse which has, in all cells, sites of recognition for said Cre recombinase protein flanking said DNA sequence(s) of interest;

d) crossing said fertile adult mouse with a transgenic mouse in which targeted cells expresses said fusion protein and obtaining the progeny derived from said crossing; and

e) selecting, among the progeny, said transgenic mouse.

72. (New) A method of producing a transgenic mouse according to step a) of Claim 69, comprising the following steps:

a) obtaining an embryonic stem (ES) cell modified by insertion of recognition sites for said Cre recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) introducing said modified embryonic stem cell into an embryo of said mouse;

c) developing said embryo up to the stage of a fertile adult mouse, comprising (i) implanting said embryo into the oviduct of a foster mother mouse to produce a chimeric mouse; and (ii) breeding of said chimeric mouse with a wild-type mouse to produce a mouse which has, in all cells, sites of recognition for said Cre recombinase protein flanking said DNA sequence(s) of interest;

d) introducing said fusion protein into targeted cells of said fertile adult mouse.

73. (New) A method of producing a transgenic mouse according to step a) of Claim 69, comprising the following steps:

a) obtaining a somatic cell modified by insertion of site(s) of recognition for said Cre recombinase protein into said DNA sequence(s) of interest, located in one or more chromosomes, by homologous recombination;

b) transferring the nucleus of said modified somatic cell into the cytoplasm of an enucleated recipient oocyte;

c) developing the embryo obtained in step b) up to the stage of a fertile adult mouse, comprising (i) implanting said embryo into the oviduct of a foster mother mouse to produce a chimeric mouse; and (ii) breeding of said chimeric mouse with a wild-type mouse to produce a mouse which has, in all cells, sites of recognition for said Cre recombinase protein flanking said DNA sequence(s) of interest;

d) introducing said fusion protein into targeted cells of said fertile adult mouse.

74. (New) The method of Claim 69, wherein said one or more sites of recognition specific for said Cre recombinase protein comprise the sequences Lox P.

75. (New) The method of Claim 69, wherein said hinge region comprises all or part of the D hinge region of a nuclear estrogen receptor.

76. (New) The method of Claim 69, wherein said hinge region comprises amino acids 282 to 301 of the sequence of SEQ ID NO. 2.

77. (New) The method of Claim 69, wherein said polypeptide chosen from the ligand-binding domain of the nuclear human estrogen receptors is the ligand-binding domain of the human nuclear estrogen receptor α and in that said ligand-binding domain exhibits at least the following mutations:

- mutation (G400V) glycine to valine at position 400 of the sequence SEQ ID No. 2;
- mutation (methionine-leucine) to (alanine-alanine) situated at position 543-544 (M543A/L544A mutation) of the sequence SEQ ID No. 2.

78. (New) The method of Claim 69, wherein said fusion protein is encoded by a fusion gene integrated into one or more of the chromosomes of said cell of said mouse, said fusion gene being under the control of expression elements ensuring its expression in targeted cells of said mouse.

79. (New) The method of Claim 78, wherein said expression elements are chosen from elements controlling tissue-specific and cell-specific expression or ubiquitous expression.

80. (New) The method of claim 78, wherein said expression elements controlling expression are chosen from elements controlling expression ensuring constitutive expression or elements controlling expression ensuring inducible expression.

81. (New) The method of Claim 78, wherein said expression element is chosen from the group composed of the promoter regions of cytokeratin 14 (K 14), of cytokeratin 5 (K 5), and of the adipocyte fatty acid binding protein 2 (aP2).

82. (New) The method of Claim 69, wherein said fusion gene having the sequence SEQ ID No. 5 encodes the fusion protein Cre-ER^{T2} having the sequence SEQ ID No. 6.

83. (New) The method of Claim 69, wherein said DNA sequence of interest is a gene comprising RXR_{α}.

84. (New) The method of Claim 69, wherein targeted cells of said mouse comprise:

- a fusion gene encoding the fusion protein Cre-ER^{T2} having the sequence ID No. 6, said fusion gene being under the control of the adipocyte fatty acid binding protein 2 (aP2) promoter region;
- one or more chromosomal DNA sequences of interest in their natural chromatin context and flanked ("floxed") on each side by a one lox site, the two lox sites being oriented as a direct repeat.

85. (New) The method of Claim 69, wherein the synthetic ligand endowed with antiestrogenic activity is selected from the group consisting of Tamoxifen, 4-hydroxyTamoxifen, ICI 164 384 and ICI 182 780.

86. (New) The method of Claim 85, wherein the synthetic ligand endowed with antiestrogenic activity is Tamoxifen or 4-hydroxyTamoxifen.